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Risk factors of chronic kidney disease progression: Dutch cohort studies

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Chapter 3 –

Body-fat indicators and kidney function decline in older post-myocardial infarction patients: The Alpha Omega Cohort study

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ABSTRACT

Background: Obesity increases risk of hypertension and diabetes, the leading causes of end-stage renal disease. The effect of obesity on kidney function decline in stable post-myocardial infarction (MI) patients is poorly documented. This relation was investigated in a large cohort of older post-MI patients.

Design: Data were analyzed from 2410 post-MI patients in the Alpha Omega Trial, aged 60–80 years receiving optimal pharmacotherapy treatment (79% men, 18% diabetes).

Methods: Cystatin C based estimated glomerular filtration rate ($eGFR_{cysC}$) was calculated at baseline and after 41 months, using the CKD-EPI equation. Obesity was defined as body-mass index (BMI) ≥ 30 kg/m² and high waist circumference (WC) as ≥ 102 and ≥ 88 cm for men and women. The relation between BMI, WC and annual $eGFR_{cysC}$ decline was evaluated by linear regression.

Results: At baseline, mean (SD) $eGFR_{cysC}$ was 81.5 (19.6) ml/min/1.73m², 23% of all patients were obese. After multivariable adjustment, the annual mean (95%-CI) $eGFR_{cysC}$ decline in men and women was -1.45 (-1.59 to -1.31) and -0.92 (-1.20 to -0.63) ml/min/1.73m², respectively (P=0.001). Obese versus non-obese patients and patients with high versus normal WC experienced greater annual $eGFR_{cysC}$ decline. Men and women showed an additional annual $eGFR_{cysC}$ decline of -0.35 (-0.56 to -0.14) and -0.21 (-0.55 to 0.14) ml/min/1.73m² per 5 kg/m² BMI increment (P for interaction 0.3).

Conclusions: High compared to normal BMI or WC were associated with more rapid kidney function decline in older stable post-MI patients receiving optimal drug therapy.

INTRODUCTION

The prevalence of obesity has increased to epidemic proportions and is ranked globally in the top five risk factors for death.¹ Obesity, defined as a body mass index (BMI) of ≥ 30 kg/m², is associated with an increased risk of cardiovascular morbidity and mortality, as well as accelerated kidney function decline.¹⁻³ Impaired kidney function itself is a robust and independent risk factor for cardiovascular morbidity and mortality.⁴ The annual rate of kidney function decline in post-myocardial infarction (MI) patients is more than double that of the general population.^{5,6}

Obesity may promote kidney damage through both hemodynamic and hormonal effects. The deleterious effects of obesity on the kidney are, in part, mediated by cardiovascular risk factors such as diabetes mellitus, hypertension and dyslipidemia.¹ Additionally, accumulation of visceral fat can increase production of inflammatory mediators by adipocytes, contributing to glomerular and interstitial fibrosis.⁷ Furthermore, obesity is associated with an increase in the single-nephron glomerular filtration rate, which may lead to glomerulosclerosis and subsequent progressive loss of kidney function.⁸

Several studies have suggested a paradoxical effect of obesity in individuals with pre-existing chronic illness, such as chronic kidney disease, showing that obesity is associated with improved survival or kidney function.^{9,10} This “obesity paradox” challenges current guidelines, which advise weight reduction towards an ideal BMI of 20–25 kg/m².¹¹

The aim of this study was to assess the association between obesity and the rate of kidney function decline in older post-MI patients receiving state-of-the-art drug treatment, separately for men and women, who differ in body composition. These results might inform care guidelines for post-MI patients.

METHODS

Study design

This is a secondary analysis of the prospective Alpha Omega Cohort study (ClinicalTrials.gov no. NCT03192410). The cohort consists of patients included in the Alpha Omega Trial, a randomized controlled trial of omega-3 (n-3) fatty acid supplementation undertaken in 4837 patients aged 60–80 years with a verified history of MI. Patients received state-of-the-art antihypertensive, antithrombotic and lipid-modifying drug treatment, as described in detail elsewhere.¹² The trial started in 2002 and ended in 2009. For this study, patients were selected from whom non-fasting blood was drawn at baseline and after

41 months. Owing to financial constraints, two blood samples were obtained in only 2426 patients (50% of the cohort), i.e. those randomized before August 2005. Of all patients randomized prior to August 2005 (n=2918), 233 patients died during follow-up, 259 patients had missing blood samples or declined to participate, and 16 patients had missing data on BMI and/or waist circumference (WC), yielding an evaluable cohort of 2410 patients (Supplementary Figure S1). The study was conducted in accordance with the Helsinki Declaration and was approved by a central and local medical ethics committee in the Netherlands. Written informed consent was obtained from all patients.

Body mass index and waist circumference

Body weight and height were measured with the subject wearing light indoor clothing without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Following World Health Organization (WHO) guidelines, normal weight was defined as a BMI of 18.5–24.9 kg/m², overweight as a BMI of 25.0–29.9 kg/m² and obesity as a BMI of 30.0 kg/m² or greater.¹ WC, measured at the midpoint between the bottom rib and the top of the hipbone, was used as a proxy of visceral fat. Men with a WC ≥102 cm and women with a WC ≥88 cm were considered to have a high risk of metabolic complications, hereafter referred to as high, as opposed to normal, WC.¹

Kidney function assessment

At baseline and after 41 months follow-up we measured from stored blood serum cystatin C (cysC) using a particle-enhanced immunonephelometric assay and serum creatinine (cr) by the modified kinetic Jaffé method, as previously described in detail.⁴ We estimated glomerular filtration rate (eGFR) with cysC alone and the combined cr-cysC Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012, taking into account age, sex and race.¹³ In the main analyses results are shown for eGFR_{cysC}, as it is recommended for confirmatory testing in the current KDIGO guidelines.¹¹ In the supplements the results are presented for eGFR_{cr-cysC}. The change (or slope) of the eGFR_{cysC} and eGFR_{cr-cysC} from baseline to 41 months was calculated for each patient by subtracting the eGFR at baseline from the eGFR after 41 months. Assuming a linear kidney function decline during follow-up, we then calculated an annual decline rate. Rapid kidney function decline was defined as an annual eGFR_{cysC} decline of ≥3 mL/min/1.73m².¹⁴

Data collection

Patients were interviewed and physically examined by trained research nurses at home or in the hospital at baseline and after 41 months. Lipid, glucose and high-sensitivity C-reactive protein (hsCRP) levels were determined as described elsewhere.¹⁵ Information on demographic variables, lifestyle habits, current health status, and medical history were collected by self-administered questionnaires, as previously described.¹² Questionnaires were checked by research nurses. Diabetes mellitus was considered present in case of a self-reported physician diagnosis, use of glucose-lowering drugs, and/or elevated blood glucose. We used the average of two blood pressure measurements after a 10 min seated rest. Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

Data analysis

Baseline characteristics are presented as mean (SD), median (interquartile range), or number (percentage) as appropriate. Missing data on level of education ($n=14$) were imputed by the sex-specific mode. The relation between BMI or WC and kidney function decline met the linear regression assumptions. ANCOVA was used to calculate mean annual eGFR decline rates per WHO category of BMI and for high and normal WC. Normal BMI or normal WC was applied as the reference category. In these analyses, 2 patients with a BMI <18.5 kg/m² were excluded. Linear regression was used to study the association between BMI or WC as continuous variables and kidney function decline. Regression coefficients were calculated per 5 kg/m² increment of BMI (approximately 1 SD), corresponding to the width of each WHO category; and per 10 cm increment of WC, which approximately corresponds to a 5 kg/m² increment of BMI.¹⁶

The continuous relation between each indicator of body fat (BMI and WC) and kidney function decline was further analyzed in a flexible manner using four-knot restricted cubic splines with 95% confidence intervals (CIs). As per general guidelines, the knots were chosen at the 5th, 35th, 65th and 95th percentile of the BMI and WC distribution for men and women separately.¹⁷

All analyses were adjusted for the n-3 fatty acid treatment groups of the Alpha Omega Trial (three dummy variables). In addition to the treatment group, we adjusted for age at baseline and sex (model 1). According to the WHO, smoking of cigarettes, alcohol consumption and socio-economic status may confound the association of obesity with outcome.¹ Therefore, in model 2 (full model), an additional adjustment was made for these baseline factors: current cigarette smoking (yes, no), alcohol use (yes, no), and level of education (elementary education, low, intermediate and high education) as a proxy for socio-economic status. Analyses were not adjusted for baseline eGFR, since baseline-adjustment

in models with change-scores as outcome variable results in biased estimates.¹⁸ In the main analyses we did not control for variables considered likely causal intermediates in the relation between obesity and kidney function decline, such as blood pressure, diabetes, and low-density lipoprotein (LDL)-cholesterol.

Sensitivity analyses

Several sensitivity analyses were performed. First, we included factors in the causal pathway, diabetes, systolic blood pressure and LDL-cholesterol, to estimate the presence of mediation. In a separate analysis we controlled for use of renin-angiotensin system (RAS) blocking drugs and physical activity. We explored the presence of effect measure modification between treatment group and BMI or WC with regard to kidney function decline. Finally, we investigated the potential relation between change in BMI or WC from baseline to 41 months follow-up and annual eGFR decline. The main analyses were repeated using eGFR_{cr-cysC} decline as outcome.¹⁴ All results are presented for men and women separately, given previously reported differences in kidney function decline between men and women.

Two-sided P-values <0.05 were considered statistically significant. All analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, IL, USA) and STATA Statistical Software (Statacorp, College Station, TX, USA), version 14.1.

RESULTS

Baseline characteristics

Of all patients, mean age was 69 years, 79% were men, and 99% were white, median time since MI was 4.0 years. Baseline characteristics according to BMI categories (normal weight, overweight, and obesity) are presented in Table 1. Patients with overweight or obesity compared to normal weight had more often diabetes, used more often blood pressure lowering drugs, had higher serum cholesterol levels, higher hsCRP levels and lower baseline eGFR_{cysC}. A similar trend was observed when comparing low and high WC categories (Supplementary Table S1). Mean (SD) baseline BMI was 27.5 (3.3) kg/m² for men and 28.4 (4.6) kg/m² for women. Mean (SD) WC at baseline was 102 (9) cm for men and 97 (12) cm for women. Women compared to men had more often diabetes, used more often blood pressure lowering drugs (Supplementary Table S2). BMI and WC were strongly correlated (Pearson correlation coefficient 0.8). Each 1 kg/m² increment of BMI was associated with an additional 2.2 (95% CI 2.1 to 2.3) cm increment of WC.

Table 1: Baseline characteristics of 2408 post-myocardial infarction patients, stratified by three categories of weight status according to the WHO classification.

	Normal weight (n=527)	Overweight (n=1328)	Obese (n=553)
Age, years	69.3 ± 5.4	69.0 ± 5.4	68.0 ± 5.5
Men, no (%)	419 (79.5)	1116 (84.0)	379 (68.5)
Ethnicity, white, no. (%)	522 (99.1)	1310 (98.6)	548 (99.1)
Higher education, ^a n (%)	77 (14.6)	171 (12.9)	49 (8.9)
Current smoking, no. (%)	106 (20.1)	188 (14.2)	89 (16.1)
Alcohol use, ^b n (%)	388 (73.6)	1004 (75.6)	352 (63.7)
Height, cm	172.5 ± 7.9	173.1 ± 7.8	170.0 ± 8.8
Weight, kg	69.6 ± 7.8	82.0 ± 8.3	94.7 ± 11.7
Body mass index, kg/m ²	23.3 ± 1.4	27.3 ± 1.4	32.7 ± 2.7
Waist circumference, cm	91.6 ± 7.3	100.9 ± 6.7	111.3 ± 9.2
Physically active, ^c n (%)	119 (22.6)	319 (24.0)	92 (16.6)
Time since myocardial infarction, yr	3.6 (1.6–6.1)	4.0 (2.0–6.3)	4.5 (2.4–6.9)
Diabetes, ^d n (%)	65 (12.3)	217 (16.3)	162 (29.3)
Systolic blood pressure, mmHg	141.3 ± 21.8	144.3 ± 21.4	142.8 ± 20.7
Diastolic blood pressure, mmHg	79.4 ± 10.6	82.0 ± 10.7	82.0 ± 10.5
Antihypertensive drugs, ^e n (%)	449 (85.2)	1141 (85.9)	505 (91.3)
ACE inhibitors/ATII blockers	265 (50.3)	704 (53.0)	330 (59.7)
Beta blockers	324 (61.5)	863 (65.0)	386 (69.8)
Calcium channel blockers	97 (18.4)	248 (18.7)	117 (21.2)
Diuretics	78 (14.8)	242 (18.2)	177 (32.0)
Glucose-lowering drugs, ^f n (%)	48 (9.1)	159 (12.0)	108 (19.5)
Insulin analogues	11 (2.1)	42 (3.2)	51 (9.2)
Oral glucose-lowering drugs	39 (7.4)	131 (9.9)	81 (14.6)
Lipid-modifying drugs, ^g n (%)	454 (86.1)	1140 (85.8)	480 (86.8)
Statins	452 (85.8)	1129 (85.0)	477 (86.3)
Antithrombotic agents, ^h n (%)	516 (97.9)	1294 (97.4)	541 (97.8)
Total cholesterol, ⁱ mmol/L	4.78 ± 0.92	4.81 ± 0.94	4.95 ± 0.91
HDL, ⁱ mmol/L	1.35 ± 0.36	1.25 ± 0.31	1.19 ± 0.31
LDL, ⁱ mmol/L	2.72 ± 0.79	2.74 ± 0.80	2.77 ± 0.80
Triglycerides, ^j mmol/L	1.41 (1.04–1.91)	1.62 (1.21–2.24)	1.96 (1.51–2.73)

Table 1: Continued

	Normal weight (n=527)	Overweight (n=1328)	Obese (n=553)
Plasma glucose, ^k mmol/L	5.6 ± 1.7	5.9 ± 1.8	6.6 ± 2.4
High-sensitivity CRP, mg/L	1.24 (0.62–2.73)	1.58 (0.81–3.37)	2.60 (1.11–4.81)
Serum cystatin C, mg/L	0.96 ± 0.23	0.96 ± 0.24	1.00 ± 0.26
Serum creatinine, ^l μmol/L	88.4 ± 26.5	90.2 ± 30.1	91.1 ± 30.9
eGFR _{cysC} , ^m mL/min/1.73m ²	82.2 ± 19.3	82.3 ± 19.0	78.8 ± 20.9
eGFR _{cr-cysC} , ^m mL/min/1.73m ²	79.4 ± 18.4	79.2 ± 18.1	76.0 ± 20.0

Data are reported as number of patients (%), mean ± SD or median (interquartile range).

ACE, angiotensin-converting enzyme; ATII, angiotensin II; cr, creatinine; CRP, C-reactive protein; cysC, cystatin C; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent task.

Two patients with BMI < 18.5 kg/m² were not reported in this table.

^a Defined as higher vocational education or university.

^b Defined as ≥ 1 glass per week.

^c Defined as three or more metabolic equivalent task (METs) during ≥ 5 days/week.

^d Self-reported diagnosis by a physician, use of glucose-lowering drugs, or in case of elevated plasma glucose level (≥ 126 mmol/L in the case of patients who had fasted 4 hours or ≥ 200 mmol/L in the case of non-fasting patients).

^e Blood pressure-lowering drugs: Anatomical Therapeutic Chemical Classification System (ATC) codes C02, C03, C07, C08, and C09.

^f Glucose-lowering drugs: ATC code A10, A10A, A10B, A10X.

^g Lipid-modifying drugs: ATC code C10, C10AA.

^h Antithrombotic agents: ATC code B01.

ⁱ To convert the values for cholesterol to mg/dL, divide by 0.02586.

^j To convert the values for triglycerides to mg/dL, divide by 0.01129.

^k To convert the values for glucose to mg/dL, divide by 0.05551.

^l To convert the values for creatinine to mg/dL, divide by 88.40.

^m eGFR_{cysC} and eGFR_{cr-cysC} based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012.¹³

Baseline kidney function

At baseline, mean (SD) eGFR_{cysC} was 83.3 (19.3) mL/min/1.73m² for men and 74.3 (18.8) mL/min/1.73m² for women. In obese compared to normal weight men and women the mean eGFR_{cysC} was 81.1 versus 84.5 mL/min/1.73m² (P=0.006), and 69.1 versus 78.1 mL/min/1.73m² (P<0.001), respectively. Men with a high WC (≥102 cm) had a mean eGFR_{cysC} of 81.8 mL/min/1.73m² compared to 84.9 mL/min/1.73m² in those with normal WC (<102 cm) (P<0.001). Women with high WC (≥88 cm) and normal WC (<88 cm) had mean eGFR_{cysC} values of 73.6 and 76.8 mL/min/1.73m² (P=0.08).

Body mass index and kidney function decline

After 41 months of follow-up, mean (95% CI) decline in eGFR_{cysC} was -4.61 (-5.06 to -4.17) mL/min/1.73m². Assuming a linear decline in kidney function, this corresponds to an annual decline of -1.34 mL/min/1.73m². Men and women had an annual eGFR_{cysC} decline of -1.45 and -0.92 mL/min/1.73m², respectively (mean difference 0.53, 95% CI: 0.22 to 0.85). Annual rates of kidney function decline for normal weight, overweight and obese patients were -1.25, -1.30 and -1.59 mL/min/1.73m², respectively (Table 2). Rapid annual kidney function decline was observed in 25% of obese patients and 23% of normal weight patients (P=0.23). Obese versus normal weight men had an additional annual eGFR_{cysC} decline of -0.42 (-0.85 to 0.02), corresponding to an additional 30% decline in kidney function. Obese versus normal weight women had an additional annual eGFR_{cysC} decline -0.35 (-1.22 to 0.53) mL/min/1.73m², corresponding to an additional 45% decline in kidney function. Each 5 kg/m² increment of BMI was associated with an additional annual eGFR_{cysC} decline of -0.35 mL/min/1.73m² in men and -0.21 mL/min/1.73m² in women, corresponding to 25% and 28% of the sex-specific mean annual kidney function decline in normal weight patients (Table 3). Supplementary Table S3 shows the adjusted analysis in more detail. Figure 1A depicts the continuous relation between BMI and annual kidney function decline for men and women. There was no effect measure modification between BMI and sex with regard to kidney function decline.

Table 2: Mean (95% CI) annual cystatin C based kidney function decline (mL/min/1.73m²) in 2408 post-myocardial infarction patients according to BMI and WC category, overall and for men and women separately.

	All patients	Normal weight ^a (ref)	Overweight	Obesity	Normal WC ^b (ref)	High WC
All patients	n=2408	n=527	n=1328	n=553	n=1022	n=1386
Crude	-1.34 (-1.46; -1.21)	-1.25 (-1.53; -0.98)	-1.33 (-1.50; -1.15)	-1.46 (-1.73; -1.19)	-1.19 (-1.38; -0.99)	-1.45 (-1.62; -1.29)
Model 1		-1.25 (-1.53; -0.98)	-1.29 (-1.47; -1.12)	-1.60 (-1.87; -1.33)	-1.19 (-1.38; -0.99)	-1.57 (-1.75; -1.39)
Model 2		-1.25 (-1.53; -0.98)	-1.30 (-1.48; -1.13)	-1.59 (-1.87; -1.32)	-1.19 (-1.38; -0.99)	-1.57 (-1.74; -1.39)
Men	n=1914	n=419	n=1116	n=379	n=914	n=1000
Crude	-1.45 (-1.59; -1.31)	-1.38 (-1.68; -1.09)	-1.39 (-1.58; -1.21)	-1.69 (-2.00; -1.38)	-1.25 (-1.46; -1.05)	-1.63 (-1.82; -1.44)
Model 1		-1.38 (-1.69; -1.09)	-1.41 (-1.59; -1.22)	-1.82 (-2.14; -1.51)	-1.25 (-1.46; -1.05)	-1.65 (-1.84; -1.45)
Model 2		-1.38 (-1.69; -1.09)	-1.41 (-1.59; -1.23)	-1.80 (-2.12; -1.49)	-1.25 (-1.46; -1.05)	-1.63 (-1.82; -1.44)
Women	n=494	n=108	n=212	n=174	n=108	n=386
Crude	-0.92 (-1.20; -0.63)	-0.75 (-1.42; -0.08)	-0.97 (-1.45; -0.49)	-0.96 (-1.49; -0.43)	-0.61 (-1.28; 0.06)	-1.00 (-1.36; -0.65)
Model 1		-0.75 (-1.42; -0.08)	-0.92 (-1.44; -0.44)	-0.94 (-1.47; -0.40)	-0.61 (-1.28; 0.06)	-0.95 (-1.32; -0.59)
Model 2		-0.75 (-1.42; -0.08)	-1.03 (-1.54; -0.53)	-1.09 (-1.66; -0.52)	-0.61 (-1.28; 0.06)	-1.01 (-1.38; -0.64)

BMI, body-mass index; CI, confidence interval; WC, waist circumference.

Normal weight BMI 18.5 - 24.9, overweight BMI 25.0 - 29.9, obesity BMI ≥ 30.0 kg/m². Normal and high WC <88 and ≥ 88 cm for women and <102 and ≥ 102 cm for men. Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2012.²³

Two patients with BMI < 18.5 kg/m² were not reported in this table. Adjusted variables were fixed at the mean value of the reference group, hence the results of the reference category are equal across models.

^a Reference: annual kidney function decline in normal weight patients.

^b Reference: annual kidney function decline in normal WC patients.

Model 1: adjusted for treatment group, age and sex.

Model 2: model 1 plus additional adjustment for current smoking, alcohol use, level of education.

Table 3: Association of BMI and WC with annual cystatin C based kidney function decline in 2410 post-myocardial infarction patients, overall and for men and women separately.

	Additional annual eGFR _{cysc} decline, mean (95%-CI)		
	Total, n=2410	Men, n=1914	Women, n=496
Per 5 kg/m ² increment of BMI			
Crude	-0.20 (-0.37; -0.02)	-0.27 (-0.48; -0.06)	-0.15 (-0.48; 0.19)
Model 1	-0.28 (-0.46; -0.11)	-0.36 (-0.57; -0.15)	-0.15 (-0.49; 0.19)
Model 2	-0.28 (-0.46; -0.10)	-0.35 (-0.56; -0.14)	-0.21 (-0.55; 0.14)
Per 10 cm increment of WC			
Crude	-0.24 (-0.36; -0.11)	-0.19 (-0.35; -0.04)	-0.19 (-0.46; 0.08)
Model 1	-0.21 (-0.34; -0.08)	-0.21 (-0.37; -0.06)	-0.19 (-0.46; 0.08)
Model 2	-0.20 (-0.34; -0.07)	-0.21 (-0.36; -0.06)	-0.22 (-0.49; 0.06)

BMI, body-mass index; CI, confidence interval; eGFR_{cysc}, Cystatin C based estimated glomerular filtration rate; WC, waist circumference.

Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, 2012.¹³

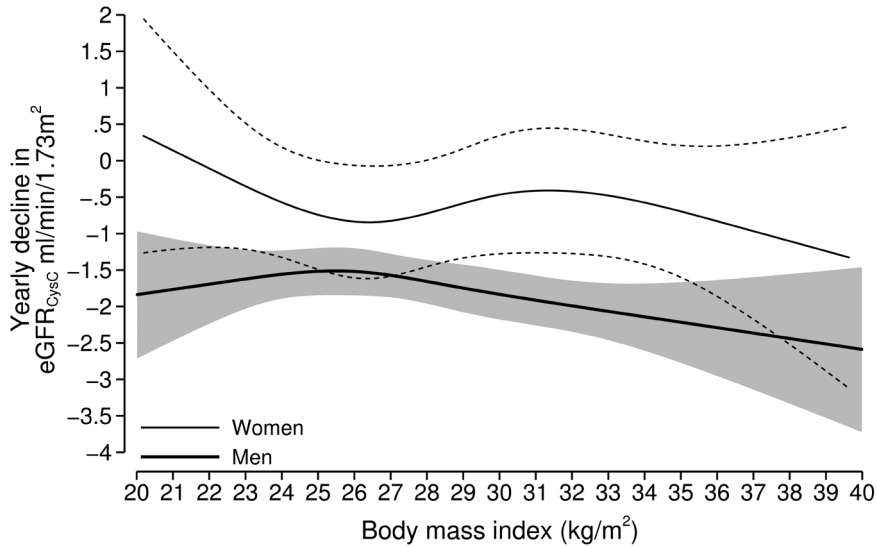
Model 1: adjusted for treatment group, age and sex.

Model 2: model 1, additionally adjusted for current smoking, alcohol use, level of education

Waist circumference and kidney function decline

Men and women with high versus normal WC had a faster annual decline in kidney function (Table 2). In men, the additional decline in eGFR (95% CI) was -0.39 (-0.66 to -0.13) mL/min/1.73m²; for women it was -0.40 (-1.17 to 0.36) mL/min/1.73m². Among patients with high and normal WC, 26% and 21% showed rapid kidney function decline, respectively (P=0.003). In regression analysis, a squared WC term was significant in men (P=0.03) but not in women (P=0.2). For each 10 cm increment of WC there was an additional annual kidney function decline of -0.21 mL/min/1.73m² in men and -0.22 mL/min/1.73m² in women (Table 3 and Supplementary Table S3). Figure 1B depicts the continuous relation between WC and annual kidney function decline for men and women.

A.



B.

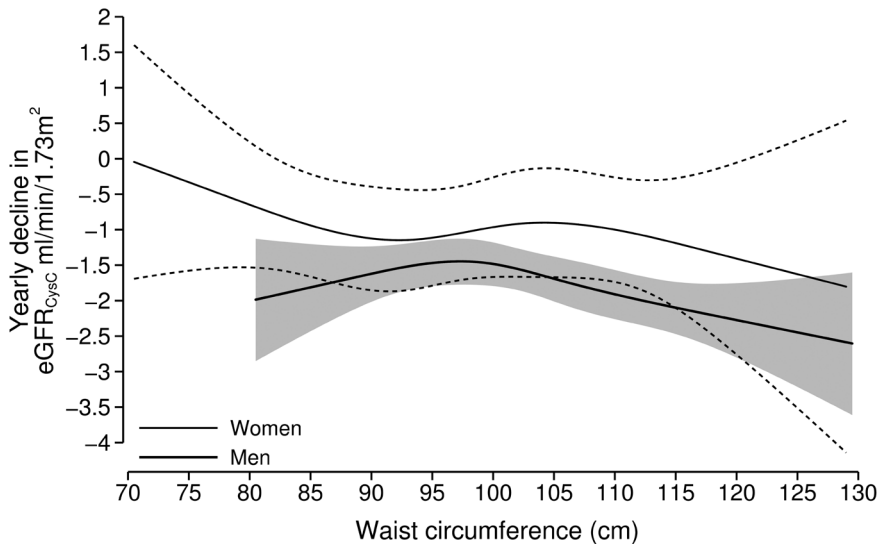


Figure 1. A. Association between body mass index (BMI) and B. waist circumference (WC) and annual kidney function decline for men and women. Linear regression coefficients for annual kidney function decline according to BMI or WC were modelled by separate restricted cubic splines. Patients with extreme values of BMI [<20 kg/m² (N=22, 0.9%) and >40 kg/m² (N=11, 0.5%)], or WC [<70 for women, <80 for men with BMI <20 kg/m² (n=2 and n=1) and >130 cm (n=18)] were excluded. The model was adjusted for age, treatment group and current smoking.

Sensitivity analyses

In addition to model 2, further adjustment for diabetes attenuated the association of BMI (and WC) with kidney function decline. The regression coefficient per 5 kg/m² BMI changed from -0.28 to -0.20 (Supplementary Table S4). Additional adjustment for systolic blood pressure or LDL-cholesterol did not change the association. Adjustment for use of RAS blocking drugs or physical activity did not essentially change the results. There was no evidence for effect modification between BMI or WC and treatment group with regard to kidney function decline (data not shown). When WC, instead of BMI, was taken as determinant, results were comparable. On average, BMI and WC did not change during follow-up, with a mean (SD) change of 0.03 (1.67) kg/m² and 0.14 (5.99) cm. Change in BMI was not associated with annual eGFR_{cysC} decline. The regression coefficient for each unit decline in BMI was -0.052 (-0.129 to 0.024). Likewise, decline in WC was not associated with eGFR_{cysC} decline. Finally, taking eGFR_{cr-cysC} as outcome, resulted in slightly weaker effect estimates (Supplementary Table S5 and S6).

DISCUSSION

This is the first study to show a progressive association between adiposity and kidney function decline in stable post-MI patients receiving optimal pharmacological treatment. The mean annual decline in kidney function was -1.45 mL/min/1.73m² for men and -0.92 mL/min/1.73m² for women. Obese men and women showed, on average, 30% and 45% faster annual kidney function decline than individuals of normal weight. Each 5 kg/m² increment of BMI was associated with an additional annual kidney function decline of -0.35 mL/min/1.73m² in men and -0.21 mL/min/1.73m² in women. Finally, men and women with high versus normal WC experienced a more rapid decline in kidney function.

The annual kidney function decline of -1.3 mL/min/1.73m² observed in our study is lower than the -2.2 mL/min/1.73m² for post-MI patients found in the Prevention of Renal and Vascular End-stage Disease study, possibly because the patients in our cohort received more optimal cardiovascular drug treatment.⁵ Other researchers have reported a mean annual eGFR decline of -1.0 mL/min/1.73m² in a community-based cohort (mean age 55 years) and -1.8 mL/min/1.73m² in healthy individuals (mean age 72 years).^{19, 20} The size of the association between high BMI and WC on kidney function decline that we found was small. However, a persistently slower kidney function decline may postpone or prevent CKD in patients at high risk, which is clinically relevant.

In addition, we recently showed in the Alpha Omega cohort a linear increase in mortality risk (cardiovascular and non-cardiovascular) for patients with an eGFR below 80 mL/min/1.73m².⁴ Preservation of kidney function is therefore important, especially in these high-risk patients.

Few studies have examined the association between BMI and kidney function decline. One study found that in younger healthy adults, being overweight or obese was associated with 1.50 and 1.85 times higher risk of rapid kidney function decline (>3% eGFR per year) compared to normal weight individuals.² Others have shown that being overweight at a younger age (26 years), compared to older age (60 years), is associated with double the risk of progression to CKD stage 3–5 by the age of 65.²¹ Interestingly, weight loss in obese patients improves kidney function. In morbidly obese patients aged between 18 and 60 years old with glomerular hyperfiltration, kidney function normalized after weight loss by gastric bypass surgery.²² We found no association between change in BMI and kidney function decline. However, BMI hardly changed during the relative short follow-up and we had no information whether weight loss was intentional or not. In our study, men had a faster rate of kidney function decline compared to women at each BMI level, but we found no effect modification. In contrast, one meta-analysis found that obese women versus men had a higher risk of CKD compared to normal-weight individuals.²³

In addition to BMI, we evaluated the effect of WC, since it is a more accurate measure for visceral fat.¹ The correlation coefficient of 0.8 between BMI and WC observed here was similar to that seen in a study which assessed patients with metabolic syndrome (mean age 68 years).^{24,25} In line with our results, others reported that individuals with high versus low WC had a 24% versus 20% risk of annual eGFR decline of >5%, in a multi-ethnic non-diabetic population.²⁵ We found for men an indication of an inverse U-shaped association between WC (or BMI) and eGFR_{cysC} decline. A possible explanation is that low weight can be a proxy of underlying disease, which is particularly relevant in elderly patients. However, the wide 95% confidence intervals reflect the great uncertainty for the lower ranges of WC and BMI.

In contrast to our results, some studies have shown that overweight or mild obesity is reno-protective compared to normal weight, both in patients with eGFR <60 or ≥60 mL/min/1.73m².^{9,10} In contrast to our study, this cohort consists of US army veterans (95% men, mean age 73y), with a lower mean eGFR of 48 mL/min/1.73m², and a large prevalence of malignancies and lung disease. Moreover, these studies did not control for smoking, which may have contributed to an underestimation of the effect of obesity, while smokers in general have lower BMI.²⁶

Various mechanisms have been proposed through which overweight and obesity could promote accelerated loss of kidney function, in addition to diabetic and hypertensive nephropathy. Obesity is associated with a state of low-grade systemic inflammation, and has been shown to cause kidney damage and eventually fibrosis via the activity of pro-inflammatory cytokines such as transforming growth factor β .²⁷

This study has limitations. First, the study design is observational, and therefore no causal inferences can be made. Second, we estimated kidney function at only two time points, which reduces precision of the estimates. Third, we did not measure kidney function directly. However, direct measurement of GFR is cumbersome, expensive, and rarely available in large epidemiological studies, and several reports have suggested that even iothalamate measurement can have daily variations of up to 8%.²⁸ Fourth, no information was available on proteinuria, an important predictor of kidney function decline. Finally, our results are applicable to post-MI patients and may therefore not be generalizable to other populations. However, both the prevalence of obesity and the prevalence of cardiovascular disease show an increasing trend worldwide, and our cohort of patients therefore represents a growing patient group.

The study has several strengths. First, to our knowledge this is the only large study that explored the association of both BMI and WC with kidney function decline in post-MI-patients receiving optimal pharmacological drug treatment, and for men and women separately. Second⁴, we measured cysC, which is currently the most accurate marker to estimate GFR, and in contrast to creatinine based eGFR is most likely not affected by glomerular hyperfiltration.^{11, 29}

In conclusion, we found in older stable post-MI patients that high BMI and WC were associated with progressive cysC-based kidney function decline, despite cardiovascular drug treatment with antihypertensive, cholesterol-lowering, antithrombotic and glucose-lowering drugs. Further research is needed to study whether prevention of obesity or weight loss intervention on-top of cardiovascular drug treatment can slow down the accelerated kidney function decline in post-MI patients.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

KE, JG, EG, DK and EH contributed to conception and design of the manuscript. KE, JG, EG, DK and EH contributed to acquisition, analysis and interpretation, and drafted the manuscript. TS, FD and JF contributed to interpretation. All authors critically revised the manuscript, all gave final approval and all agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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SUPPLEMENTARY DATA

Table S1: Baseline characteristics of 2410 post-myocardial infarction patients, stratified by normal and high waist circumference, according to the sex-specific WHO classification.

	Waist circumference Normal (n=1024)	High (n=1386)
Age, years	68.8 ± 5.3	68.9 ± 5.5
Men, no.(%)	914 (89.3)	1000 (72.2)
Ethnicity, white, no. (%)	1010 (98.6)	1372 (99.0)
Higher education, ^a no. (%)	153 (14.9)	144 (10.4)
Current smoking, no. (%)	169 (16.5)	215 (15.5)
Alcohol use, ^b n (%)	791 (77.2)	953 (68.8)
Height, cm	172.3 ± 7.5	172.2 ± 8.6
Weight, kg	74.8 ± 8.9	87.6 ± 11.9
Body mass index, kg/m ²	25.2 ± 2.2	29.5 ± 3.4
Waist circumference, cm	93.7 ± 6.5	106.8 ± 8.4
Physically active, ^c n (%)	256 (25.0)	274 (19.8)
Time since myocardial infarction, yr	3.9 (1.8–6.3)	4.1 (2.1–6.6)
Diabetes, ^d n (%)	133 (13.0)	311 (22.4)
Systolic blood pressure, mmHg	142.8 ± 21.4	143.6 ± 21.3
Diastolic blood pressure, mmHg	80.6 ± 10.6	82.0 ± 10.7
Antihypertensive drugs, ^e n (%)	851 (83.1)	1246 (89.9)
ACE inhibitors/ATII blockers	499 (48.7)	801 (57.8)
Beta blockers	640 (62.5)	935 (67.5)
Calcium channel blockers	168 (16.4)	294 (21.2)
Diuretics	135 (13.2)	364 (26.3)
Glucose-lowering drugs, ^f n (%)	101 (9.9)	214 (15.4)
Insulin analogues	22 (2.1)	82 (5.9)
Oral glucose-lowering drugs	85 (8.3)	166 (12.0)
Lipid-modifying drugs, ^g n (%)	873 (85.3)	1203 (86.8)
Statins	866 (84.6)	1194 (86.1)
Antithrombotic agents, ^h n (%)	999 (97.6)	1354 (97.7)

Table S1: Continued

Waist circumference	Normal (n=1024)	High (n=1386)
Total cholesterol, ⁱ mmol/L	4.76 ± 0.90	4.90 ± 0.95
HDL, ⁱ mmol/L	1.29 ± 0.33	1.23 ± 0.32
LDL, ⁱ mmol/L	2.72 ± 0.78	2.76 ± 0.81
Triglycerides, ^j mmol/L	1.46 (1.09–2.00)	1.77 (1.33–2.48)
Plasma glucose, ^k mmol/L	5.7 ± 1.7	6.2 ± 2.1
High-sensitivity CRP, mg/L	1.26 (0.67–2.55)	2.15 (0.97–4.24)
Serum cystatin C, mg/L	0.95 ± 0.23	0.99 ± 0.25
Serum creatinine, ^l μmol/L	89.5 ± 27.3	90.5 ± 30.8
eGFR _{cysC} , ^m mL/min/1.73m ²	84.0 ± 18.9	79.6 ± 19.8
eGFR _{cr-cysC} , ^m mL/min/1.73m ²	80.9 ± 18.0	76.7 ± 19.0

Data are reported as number of patients (%), mean ± SD or median (interquartile range).

ACE, angiotensin-converting enzyme; ATII, angiotensin II; cr, creatinine; CRP, C-reactive protein; cysC, cystatin C; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent task.

^a Defined as higher vocational education or university.

^b Defined as ≥1 glass per week.

^c Defined as three or more metabolic equivalent task (METs) during ≥5 days/week.

^d Self-reported diagnosis by a physician, use of glucose-lowering drugs, or in case of elevated plasma glucose level (≥126 mmol/L in the case of patients who had fasted 4 hours or ≥200 mmol/L in the case of non-fasting patients).

^e Blood pressure-lowering drugs: Anatomical Therapeutic Chemical Classification System (ATC) codes C02, C03, C07, C08, and C09.

^f Glucose-lowering drugs: ATC code A10, A10A, A10B, A10X.

^g Lipid-modifying drugs: ATC code C10, C10AA.

^h Antithrombotic agents: ATC code B01.

ⁱ To convert the values for cholesterol to mg/dL, divide by 0.02586.

^j To convert the values for triglycerides to mg/dL, divide by 0.01129.

^k To convert the values for glucose to mg/dL, divide by 0.05551.

^l To convert the values for creatinine to mg/dL, divide by 88.40.

^m eGFR_{cysC} and eGFR_{cr-cysC} based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012.¹³

Table S2: Baseline characteristics of all 2410 post-myocardial infarction patients, overall and for men and women separately.

	All patients (n=2410)	Men (n=1914)	Women (n=496)
Age, years	68.9 ± 5.4	68.5 ± 5.3	70.2 ± 5.6
Ethnicity, white, no. (%)	2382 (98.8)	1894 (99.0)	488 (98.4)
Higher education, ^a no. (%)	297 (12.3)	272 (14.2)	25 (5.0)
Current smoking, no. (%)	384 (15.9)	308 (16.1)	76 (15.3)
Alcohol use, ^b n (%)	1744 (72.4)	1497 (78.2)	247 (49.8)
Height, cm	172.2 ± 8.1	174.8 ± 6.4	162.3 ± 6.2
Weight, kg	82.2 ± 12.4	84.1 ± 11.6	74.8 ± 12.6
Body mass index, kg/m ²	27.7 ± 3.6	27.5 ± 3.3	28.4 ± 4.6
Waist circumference, cm	101.2 ± 10.0	102.5 ± 9.1	96.4 ± 11.6
Physically active, ^c n (%)	530 (22.0)	442 (23.1)	88 (17.7)
Time since myocardial infarction, yr	4.0 (2.0–6.4)	4.1 (2.1–6.6)	3.5 (1.7–6.1)
Diabetes, ^d n (%)	444 (18.4)	330 (17.2)	114 (23.0)
Systolic blood pressure, mmHg	143.3 ± 21.4	143.5 ± 20.9	142.3 ± 23.0
Diastolic blood pressure, mmHg	81.4 ± 10.7	81.8 ± 10.6	79.8 ± 11.1
Antihypertensive drugs, ^e n (%)	2097 (87.0)	1644 (85.9)	453 (91.3)
ACE inhibitors/ATII blockers	1300 (53.9)	1013 (52.9)	287 (57.9)
Beta blockers	1575 (65.4)	1230 (64.3)	345 (69.6)
Calcium channel blockers	462 (19.2)	362 (18.9)	100 (20.2)
Diuretics	499 (20.7)	333 (17.4)	166 (33.5)
Glucose-lowering drugs, ^f n (%)	315 (13.1)	227 (11.9)	88 (17.7)
Insulin analogues	104 (4.3)	69 (3.6)	35 (7.1)
Oral glucose-lowering drugs	251 (10.4)	186 (9.7)	65 (13.1)
Lipid-modifying drugs, ^g n (%)	2076 (86.1)	1648 (86.1)	428 (86.3)
Statins	2060 (85.5)	1633 (85.3)	427 (86.1)
Antithrombotic agents, ^h n (%)	2353 (97.6)	1875 (98.0)	478 (96.4)
Total cholesterol, ⁱ mmol/L	4.84 ± 0.93	4.75 ± 0.90	5.18 ± 0.98
HDL, ⁱ mmol/L	1.26 ± 0.33	1.22 ± 0.30	1.41 ± 0.37
LDL, ⁱ mmol/L	2.74 ± 0.80	2.71 ± 0.78	2.88 ± 0.84
Triglycerides, ^j mmol/L	1.63 (1.22–2.28)	1.62 (1.20–2.25)	1.65 (1.27–2.39)
Plasma glucose, ^k mmol/L	6.0 ± 2.0	6.0 ± 1.9	6.1 ± 2.2

Table S2: Continued

	All patients (n=2410)	Men (n=1914)	Women (n=496)
High-sensitivity CRP, mg/L	1.66 (0.82–3.61)	1.52 (0.80–3.33)	2.28 (0.93–4.48)
Serum cystatin C, mg/L	0.97 ± 0.24	0.96 ± 0.24	1.00 ± 0.27
Serum creatinine, ^l μmol/L	90.1 ± 29.3	92.6 ± 29.7	79.8 ± 25.2
eGFR _{cysC} ^m mL/min/1.73m ²	81.5 ± 19.6	83.3 ± 19.3	74.3 ± 18.8
eGFR _{cr-cysC} ^m mL/min/1.73m ²	78.5 ± 18.7	80.3 ± 18.4	71.0 ± 17.8

Data are reported as number of patients (%), mean ± SD or median (interquartile range).

ACE, angiotensin-converting enzyme; ATII, angiotensin II; cr, creatinine; CRP, C-reactive protein; cysC, cystatin C; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent task.

^a Defined as higher vocational education or university.

^b Defined as ≥1 glass per week.

^c Defined as three or more metabolic equivalent task (METs) during ≥5 days/week.

^d Self-reported diagnosis by a physician, use of glucose-lowering drugs, or in case of elevated plasma glucose level (≥126 mmol/L in the case of patients who had fasted 4 hours or ≥200 mmol/L in the case of non-fasting patients).

^e Blood pressure-lowering drugs: Anatomical Therapeutic Chemical Classification System (ATC) codes C02, C03, C07, C08, and C09.

^f Glucose-lowering drugs: ATC code A10, A10A, A10B, A10X.

^g Lipid-modifying drugs: ATC code C10, C10AA.

^h Antithrombotic agents: ATC code B01.

ⁱ To convert the values for cholesterol to mg/dL, divide by 0.02586.

^j To convert the values for triglycerides to mg/dL, divide by 0.01129.

^k To convert the values for glucose to mg/dL, divide by 0.05551.

^l To convert the values for creatinine to mg/dL, divide by 88.40.

^m eGFR_{cysC} and eGFR_{cr-cysC} based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012.¹³

Table S3: Association of BMI and WC with annual cystatin C based kidney function decline in 2410 post-MI patients. Analyses are adjusted one by one for confounding factors.

Model	BMI, per 5 kg/m ²	WC, per 10 cm
Crude	-0.20 (-0.37 to -0.02)	-0.24 (-0.36 to -0.11)
Treatment group	-0.20 (-0.37 to -0.02)	-0.23 (-0.36 to -0.11)
Model 1	-0.27 (-0.45 to -0.09)	-0.21 (-0.34 to -0.08)
Model 1 + smoking	-0.29 (-0.46 to -0.11)	-0.21 (-0.34 to -0.08)
Model 1 + alcohol use	-0.28 (-0.46 to -0.10)	-0.21 (-0.34 to -0.07)
Model 1 + education	-0.28 (-0.45 to -0.10)	-0.20 (-0.33 to -0.07)
Model 2 (full model)	-0.28 (-0.46 to -0.10)	-0.20 (-0.34 to -0.06)

BMI, body-mass index; WC, waist circumference.

Model 1: adjusted for treatment group, age and sex.

Model 2: model 1 plus additional adjustment for current smoking, alcohol use, and level of education.

Table S4: Association of BMI and WC with annual cystatin C based kidney function decline in 2410 post-MI patients. Analyses are adjusted for factors in the causal path (diabetes, systolic blood pressure, LDL-cholesterol).

Model	BMI, per 5 kg/m ²	WC, per 10 cm
Crude	-0.20 (-0.37 to -0.02)	-0.24 (-0.36 to -0.11)
Model 1	-0.27 (-0.45 to -0.09)	-0.21 (-0.34 to -0.08)
Model 2	-0.28 (-0.46 to -0.10)	-0.20 (-0.34 to -0.06)
Model 2 + diabetes	-0.20 (-0.38 to -0.02)	-0.14 (-0.28 to -0.01)
Model 2 + systolic blood pressure	-0.27 (-0.45 to -0.09)	-0.20 (-0.33 to -0.07)
Model 2 + LDL	-0.28 (-0.47 to -0.10)	-0.20 (-0.34 to -0.06)

BMI, body-mass index; LDL, low-density lipoprotein; WC, waist circumference

Model 1: adjusted for treatment group, age and sex.

Model 2: model 1 plus additional adjustment for current smoking, alcohol use, and level of education.

Table S5: Mean (95% CI) annual creatinine-cystatin C based kidney function decline (mL/min/1.73m²) in 2328 post-myocardial infarction patients according to BMI or WC category, overall and for men and women separately.

	All patients	Normal weight (ref)	Overweight ^a	Obesity ^a	Normal WC (ref)	High WC ^b
All patients	n=2328	n=511	n=1288	n=529	n=996	n=1332
Crude	-1.73 (-1.89 to -1.58)	-1.71 (-2.04 to -1.39)	-1.67 (-1.88 to -1.47)	-1.92 (-2.24 to -1.60)	-1.63 (-1.86 to -1.39)	-1.82 (-2.02 to -1.62)
Model 1	-1.71 (-2.04 to -1.39)	-1.66 (-1.86 to -1.45)	-1.66 (-1.86 to -1.45)	-1.94 (-2.27 to -1.62)	-1.63 (-1.86 to -1.39)	-1.79 (-2.01 to -1.58)
Model 2	-1.71 (-2.04 to -1.39)	-1.66 (-1.86 to -1.45)	-1.66 (-1.86 to -1.45)	-1.93 (-2.26 to -1.60)	-1.63 (-1.86 to -1.39)	-1.79 (-2.00 to -1.57)
Men	n=1877	n=416	n=1092	n=369	n=902	n=975
Crude	-1.70 (-1.86 to -1.54)	-1.73 (-2.07 to -1.38)	-1.66 (-1.87 to -1.45)	-1.80 (-2.16 to -1.44)	-1.62 (-1.85 to -1.39)	-1.78 (-2.00 to -1.56)
Model 1	-1.73 (-2.07 to -1.38)	-1.66 (-1.87 to -1.45)	-1.66 (-1.87 to -1.45)	-1.88 (-2.25 to -1.51)	-1.62 (-1.85 to -1.39)	-1.79 (-2.01 to -1.56)
Model 2	-1.73 (-2.07 to -1.38)	-1.66 (-1.87 to -1.45)	-1.66 (-1.87 to -1.45)	-1.86 (-2.23 to -1.49)	-1.62 (-1.85 to -1.39)	-1.77 (-1.99 to -1.54)
Women	n=451	n=95	n=196	n=160	n=94	n=357
Crude	-1.86 (-2.27 to -1.45)	-1.65 (-2.55 to -0.76)	-1.72 (-2.35 to -1.10)	-2.18 (-2.87 to -1.49)	-1.68 (-2.58 to -0.78)	-1.92 (-2.38 to -1.46)
Model 1	-1.65 (-2.55 to -0.76)	-1.63 (-2.27 to -0.99)	-1.63 (-2.27 to -0.99)	-2.16 (-2.84 to -1.47)	-1.68 (-2.58 to -0.78)	-1.84 (-2.31 to -1.36)
Model 2	-1.65 (-2.55 to -0.76)	-1.63 (-2.29 to -0.98)	-1.63 (-2.29 to -0.98)	-2.31 (-3.05 to -1.56)	-1.68 (-2.58 to -0.78)	-1.88 (-2.37 to -1.39)

BMI, body-mass index; CI, confidence interval; WC, waist circumference

Normal weight BMI 18.5 - 24.9, overweight BMI 25.0 - 29.9, obesity BMI ≥30.0 kg/m². Normal and high WC <88 and ≥88 cm for women and <102 and ≥102 cm for men. Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined creatinine-cystatin C equation from 2012.¹³

^a Reference: annual kidney function decline in normal weight patients. Adjusted variables were fixed at the mean value of the reference group, hence the results of the reference category are equal across models.

^b Reference: annual kidney function decline in normal WC patients.

Model 1: adjusted for treatment group, age and sex (if not stratified for).

Model 2: model 1 plus additional adjustment for current smoking, alcohol use, level of education.

Table S6: Association of BMI and WC with annual creatinine-cystatin C based kidney function decline in 2328 post-myocardial infarction patients, overall and for men and women separately.

	Additional annual eGFR _{cr-cysC} decline, mean (95%-CI)		
	Total, n=2328	Men, n=1877	Women, n=451
Per 5 kg/m ² increment of BMI			
Crude	-0.17 (-0.38 to 0.04)	-0.17 (-0.41 to 0.07)	-0.16 (-0.60 to 0.28)
Model 1	-0.19 (-0.41 to 0.02)	-0.22 (-0.47 to 0.02)	-0.16 (-0.60 to 0.28)
Model 2	-0.19 (-0.40 to 0.02)	-0.21 (-0.46 to 0.03)	-0.22 (-0.67 to 0.23)
Per 10 cm increment of WC			
Crude	-0.12 (-0.27 to 0.04)	-0.12 (-0.29 to 0.06)	-0.19 (-0.55 to 0.16)
Model 1	-0.14 (-0.30 to 0.01)	-0.13 (-0.30 to 0.05)	-0.18 (-0.53 to 0.17)
Model 2	-0.14 (-0.30 to 0.02)	-0.12 (-0.30 to 0.05)	-0.21 (-0.57 to 0.14)

BMI, body-mass index; CI, confidence interval; eGFR_{cr-cysC}, combined creatinine-cystatin C based estimated glomerular filtration rate; WC, waist circumference.

Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) combined creatinine-cystatin C equation, 2012.¹³

Model 1: adjusted for four randomized treatment groups, age and sex (if not stratified for).

Model 2: model 1, additionally adjusted for smoking, alcohol use, level of education.

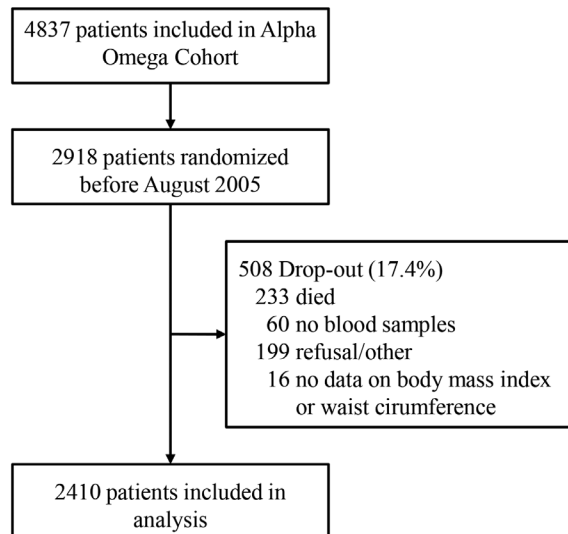


Figure S1: Flow chart of 2410 patients included in the present study. The patients randomized before August 2005 are considered a random sample of the total population of 4837 patients.

